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(54) Title: SOLUBILIZING DELIVERY SYSTEMS AND METHOD OF MANUFACTURE

(57) Abstract

Active agent/surfactant combinations are blended using selected processing conditions to at least partially place a eutectic of the combinations into intimate contact with particles of the active. The blending process enhances the solubility of the actives while allowing higher concentrations of active to be solubilized at rates than were previously possible.

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SOLUBILIZING DELIVERY SYSTEMS AND METHOD OF MANUFACTURE

Field of the Invention

The invention relates to solubilizing delivery systems in which poorly soluble materials therein dissolve readily in aqueous solutions and processes for their manufacture. More particularly the solubilizing delivery systems are combinations of an active agent/solubilizer eutectic composition in intimate contact with particles of the active agent. When active agents are pharmaceutical materials or drugs the solubilizing delivery system products may thereafter be combined with suitable amounts of conventional pharmaceutical ingredients to make comestible units or oral dosage forms, such as tablets or capsules.

Background

The preparation of drug/polymer combinations where the drug is combined with a melt of a polymer is known. These preparations include such concepts as melt mixing and extrusion.

Drugs have been blended with molten surfactants or dispersions of surfactants in order to produce solid solutions of drugs in surfactants. PCT application WO 97/02017, published January 23, 1997, shows the use of molten Pluronic surfactants as a dissolution aid for various drugs, including ibuprofen, in controlled release formulations. In the melt-blending operation disclosed therein, the drug was added to the surfactant at a temperature above the surfactant's melting point.

In literature dated 1994 and 1997, BASF Corporation discloses the production of melt extruded drug/polymer products, however no particulars of their preparation are disclosed.

In an abstract entitled "Application of Bridging Agents to Produce an Ibuprofen-Xylitol Solid Dispersion System", Greenhalgh et al. disclose the use of a Pluronic surfactant to overcome the immiscibility of ibuprofen in xylitol. They teach and disclose ibuprofen and Pluronic F68 mixtures as forming a eutectic substance having a melting point at 38°C.

According to an abstract of an article entitled "Compatibility of Ibuprofen and Ethenzamide", Drug Development and Industrial Pharmacy, Vol. 23, No. 6, 1997, pp 561-565, the chemical stability of ibuprofen and various drugs was investigated. The investigators reported that a eutectic was formed between ibuprofen and ethenzamide. In addition they reported that the chemical stability of that eutectic (with small amounts of excipents) in capsule form was found to be stable. The investigators also reported that a "remarkable" delay in dissolution was noted when the eutectic was formed above 56°C (the eutectic's melting point.)

These disclosures, however, fail to recognize, or teach the reasons for delayed dissolution of drug/ polymer (solubilizer) eutectics processed above their eutectic formation temperatures. Nor do they teach that such drug/ polymer (solubilizer) eutectics, while improving solubility of the drug, do not allow one to produce finished, marketable drug products due to the low "loading" capacity of the solubilizer, i.e., the solubilizer can only be "loaded" with relatively small amounts of active before adverse dissolution properties again come into play. Such a low "loading" of active results in oversized dosage forms to be able to deliver a sufficient amount of the active to the patient. Therefore, a need exists for high "load" drug delivery systems while still utilizing the enhanced solubilizing properties of solubilizers and surface acting agent combinations.

Summary of the Invention

The invention relates to solubilizing delivery systems and the method of producing them wherein particles of at least one active agent and at least one solubilizing agent, such as surface active agents (solubilizer), are processed at low temperatures, i.e., at temperatures below the melting points of both, and preferably from below the formation temperature of a eutectic of the active and solubilizer combination to below the temperature at which the active dissolves in the solubilizer. The processing further involves combining of ingredients at the above stated processing temperatures in the presence of forces sufficient to produce a active/solubilizer eutectic which is at least partially coated onto, or in intimate contact with, particles of the active. Preferably the particles are a crystalline form of the active ingredient at least partially surrounded or enveloped by a eutectic mixture of the active and solubilizer(s). The eutectic may also

contain crystals of the active. In the case of actives intended to be absorbed in the gut, such as Ibuprofen, the solubilizing/active systems produced by this invention have superior aqueous solubility at pH 5.2 compared to the active alone and contain from about 10% to about 95% active, and preferably from about 30% to about 90% active, and most preferably from about 40% to about 80% active.

Applicant has found that certain actives, and especially drugs will form a eutectic material with certain solubilizers when processed under sufficient forces (such as shear forces, centrifugal forces or pressure) and at temperatures from below the formation temperature of the eutectic to below the temperature at which the active dissolves in the solubilizer, or melts. These eutectics, while in the presence of the temperature and force, will coat or envelop, at least partially, particles of the active (solubilizing delivery system). This solubilizing delivery system contains a higher percentage of active than the eutectic alone is capable of while still retaining the enhanced dissolution properties of the eutectic or a combination product of the solubilizer and active. The resulting product may then be further processed (such as milling) to produce microparticles which may in turn be further processed into dosage forms of the drug.

In preferred embodiments, a drug/solubilizer solubilizing delivery system contains particles of a drug coated, at least partially, with a eutectic of the drug/solubilizer mixture. This product, upon ingestion, results in a blood plasma profile that indicates that the active is made available for uptake by the body much more quickly than drug alone would be available. In addition, the product is also able to deliver a larger amount of the drug than the eutectic alone. It is believed that during dissolution of the solubilizing delivery system the rapidly dissolving eutectic provides an initial amount of active followed by the solubilizer wetted particulate or crystalline form of the drug.

Detailed Description of the Invention

The invention relates to methods of making particulate active/solubilizer products by combining each ingredient under controlled temperature and processing conditions to yield particles of particulate (such as crystalline) actives coated with a eutectic of the active and solubilizer, and products comprising the particulate, eutectic coated solid active.

A eutectic is a combination of substances whose melting point is lower than that of any other combination of the same ingredients. Typically, eutectics melt at temperatures below the melting points of either individual ingredient.

Actives or active agents as used herein means any substance or material which one would like to improve the solubility or dissolution characteristics of. Pharmaceutical materials are the most preferred active. Such materials and ingredients will be readily apparent to the skilled artisan upon reading this invention.

In a preferred embodiment, a drug/solubilizer solubilizing delivery system of the invention, has a dissolution profile such that about 80%, or more of the drug will dissolve in water at pH 5.2 in about 5 minutes or less at 37 degrees C.

If the blend of ingredients is heated too far above the point at which the eutectic alloy forms, however, it is believed that crystals of the active ingredient dissolve in the solubilizer, or melt, resulting in a saturated or even a super saturated solution. Upon cooling the dissolved or melted active will then re-crystallize into crystals which are too large to benefit from the improved wetting of the solubilizer/eutectic coating and not dissolve as readily.

Generally, the method involves mixing from about 10% to about 95%, more preferably from about 30% to about 90%, and most preferably from about 40% to about 80% of particles of at least one active agent with from about 90% to about 5%, more preferably from about 10% to about 70%, and most preferably from about 20% to about 60% of at least one solid solubilizing agent (stabilizer) at temperatures from below the formation temperature of a eutectic of the drug/solubilizer mixture to below the temperature where the drug melts or dissolves in the solubilizer, and under sufficient forces to at least partially coat the particles of active with the eutectic material formed; and recovering the processed drug/solubilizer product. Optionally, the particle size of the recovered product can be further reduced according to known milling processes, for example. If milling or other particle size reduction methods are utilized care must be taken to insure that the temperatures created do not raise much above the original processing temperature or again, large crystals of active may form in the eutectic

The Ingredients:

A. Active Agents:

The active agent is a solid substance, preferably crystalline in nature, of generally poor water solubility. It is also preferable that the size of the particulate, or crystalline solid substance be small, preferably less than about 10μ, with less than from about 6μ being most preferred. The active agent is preferably a drug whose rapid dissolution and release is desirable, but whose solubility properties inhibit rapid dissolution. Among the useful drugs are analgesics, H2 antagonists, non-steroidal anti-inflammatory agents, anti-cholesterolemics, anti-allergy agents and anti-migraine agents. Ibuprofen (IBP), Ketoprofen and Naproxen are especially preferred drug substances.

Other useful drugs include Dextromethorphan, Chlorpheniramine Maleate, 4-Acetamidophenol (APAP), Sodium Naproxen, Diphenhydramine, Diltiazem HCl, Cimetidine, and Fexofenadine. Any active agent, or drug which forms a eutectic with the solubilizer are contemplated as being usable and encompassed by this invention.

While the action of the processing equipment may cause some attrition, its is generally desirable that the drug be supplied in a finely divided state to facilitate formation of the eutectic and coating. Ideally, the particle size of the drug before processing will be less than about 10μ, and preferably less than 6μ.

B. The Solubilizer:

The solubilizers employed generally may have both a hydrophobic and hydrophilic (HLB) character. However an important characteristic of the solubilizing agent is its ability to form a eutectic with the material it is to be processed with. In general, the melting point of the solubilizer, or combination of solubilizers should be less than the melting temperature of the active. In addition, it is preferable that there be sufficient "head room" between the solubilizer melt temperature and the active melt temperature to enable one to process the combination at a temperature sufficiently low such that the active does not dissolve in the solubilizer. It is believed that if too much of the active ingredient dissolves in the eutectic, upon cooling the active will form crystals which will be so large that they cannot benefit from the wetting effects of the solubilizer and therefore, not dissolve as readily.

For some drugs, poloxamer surfactants are particularly useful. Polyoxyethylene/polyoxypropylene surfactants, such as the Pluronics/Lutrols made by BASF Corporation, are particularly effective. Pluronic or Lutrol F68 is especially preferred. Other useful surfactants include PEG-1000, PEG 2000 and the like.

For other drugs, useful solubilizers might be salts or other pharmaceutically acceptable compounds which form a eutectic and melt at temperature lower than the drug with which they are to be combined. Among these is urea.

It is preferred that from about 90% to about 5%, more preferably from about 10% to about 70%, and most preferably from about 20% to about 60% solid solubilizer be utilized in the solubilizer delivery systems of the invention. Enough solubilizer must be present, in any event, to sufficiently coat or envelop the particles of active to enhance their dissolution.

C. The Method:

The method of the invention involves contacting solid particles of the active, including drug, and the solubilizer under conditions suitable to form the delivery system products of the invention. Following production of the products, the particulate product will generally be sized and employed, along with other pharmaceutical additives, in dosage forms.

Preferably the temperatures at which the ingredients are contacted are from below the formation point of the combination's eutectic to below the temperature at which the active will dissolve in the solubilizer so that the drug does not totally dissolve in the eutectic. When temperatures are too high, one or both of the ingredients can, upon cooling crystallize too quickly, resulting in crystal reformation which are too large to take advantage of the wetting properties of the solubilizer/eutectic.

Typical temperatures used in the invention range from at or below the standard eutectic formation temperature to below the temperature at which the active melts or readily dissolves in the solubilizer utilized. It has been found by X-ray diffraction that upon cooling crystals of the active and solubilizer form in the eutectic material. These crystals, however are very small unless the active is dissolved or present in the eutectic at too high a concentration. In addition, using the combination of temperature and force,

especially shear force, it is possible to form the eutectic and coat the particles of active at a temperature which is below the "normal" eutectic formation temperature at normal atmospheric pressure. It is also important for coating that the processing temperature be sufficiently high to control the viscosity of the mixture to allow for the forces to enable the coating of the active particles. For an Ibuprofen and Lutrol (Pluronic) F68 combination , preferred temperatures are from about 35 to about 45 degrees C.

If the temperature has to be kept low to prevent dissolving of the active, then it may be possible to encounter viscosity which makes coating difficult with an increase in the processing forces or through residence time of the materials in the presence of those forces. The forces used during processing include but are not limited to centrifugal, shear and pressure. Shear and centrifugal forces are preferred. No matter what forces the materials are subjected to, however, the forces should to be sufficient to coat the eutectic material onto crystals, or particles of the active. Generally the higher, or more intense or prolonged the forces, the more thorough the coating.

Additionally, sufficient amounts of ingredients must be used to sufficiently coat, or envelop the active particles or the enhanced dissolution properties will not be fully realized.

D. Devices:

The method of the invention is carried out on any device which provides the temperature and force conditions that facilitate eutectic formation and optional coating/encapsulation of the particles of active.

Suitable devices include extruders, flash flow spinning heads and the like. One highly preferred device is a multiple zone extruder having a length to diameter ratio L/D sufficient to coat or encapsulate particles of the active with the active/solubilizer eutectic material.

In addition, flash flow spinning heads are useful. Inside the device, the feedstock particles lose their resistance to liquid flow and become "liquiform." In this state, the eutectic is physically transformed from its original solid state, through a liquid state and back to a solid state instantaneously. While the particles undergo this transformation, they are acted upon by centrifugal force, or another shearing force, which force separates them

into discrete eutectic coated particles. U. S. Patent _______, sets out the details of the liquiflash, flash flow processes.

The solubilizing delivery system particles may thereafter be ground by known methods such as milling and optionally screened to separate particles of a size sufficient for the dosage form in which they will be included. The size reduction method should, however be monitored to prevent the delivery system particle from reaching temperatures above those used during their manufacture otherwise large crystal formation could occur. Once sized, the particles may be mixed with various pharmaceutical ingredients, e.g., sweeteners, fillers, perfumes, flow control agents, binders, and the like in suitable amounts. Such dosage forms can include tablets and capsules and other oral dosage forms.

E. The Combination:

The active agent and solubilizer are to be combined in active:solubilizer ratios of about 95:5 to 10:90, preferably about 90:10 to about 25:75, most preferably about 80:20 to about 40:60, with appropriate ratios being determined by the character of the ingredients. In general, it is preferred that the active ingredients be present in amounts that are as high as possible without detracting from the improved dissolution of the invention.

When IBP and the surfactant Lutrol (Pluronic) F68 are used in the inventive process, particles of IBP are coated (at least partially, and preferably completely) with a eutectic mixture of the IBP and Lutrol F68. 80% of the solubilizing delivery system so produced will dissolve in 37°C degree water at a pH of 5.2 in five (5) minutes as measured by a Beckman/Hanson Automated Dissolution System as described below. The preferred ratios of IBP to Lutrol F68 are from about 60:40 to about 75:25.

It is believed that combinations of such additional drugs as Ketoprofen or Naproxen and a solubilizer, or solubilizers such as Lutrol F68 with which they form a eutectic will be particularly useful.

While active agents such as drugs have been particularly discussed and are exemplified below, the invention encompasses any combination of ingredients where improved solubility or dissolution of one ingredient (the active) is beneficial. As indicated the active must also form a eutectic with a solubilizer, or combination of solubilizers which

can be coated onto particles of that ingredient. Such materials and ingredients will be readily apparent to the skilled artisan upon reading of this invention.

Examples

The following examples illustrate the method and production of the novel products of the invention and are included as examples only and not intended to limit the scope of the invention.

Example I

Poloxamer 188 NF (Lutrol F68) was milled by passing the material through an Apex 114 mill with a 20 screen with the hammers forward. The feed rate was 4 RPM with a mill speed of 4590 RPM. The mill was allowed to cool for 15 minutes and then the material was run through again at the same settings.

9.76 kg of micronized Ibuprofen (IBP) and 6.60 kg of the milled Lutrol F68 were added to a Diosna V100 mixer in the following order: (1) one-half of the solubilizer, (2) all of the IBP, (3) the remaining portion of the solubilizer. The ingredients were mixed for about five minutes at speed II with the chopper off to produce a 60:40 IBP:Lutrol mixture. This mixture was used as a feedstock as follows:

The feedstock was fed to the spinning head disclosed in U. S. Application Serial No. 08/874,215, filed June 13, 1997. The head speed was increased to 60Hz while the heating elements were raised to a temperature which produced liquiflash conditions.

The spinning head forced the material through its orifices and the product was permitted to free fall a distance of from six to eight feet below the head. It comprises eutectic coated particles containing 60:40 IBP:solubilizer.

Example II

The same IBP/Lutrol F68 mixture as in Example I was made up as described in Example I. Instead of processing the mixture in a spinning head, however, an extruder manufactured by AVP was used as follows:

Set up the APV extruder with the water bath set to 20°C, and the heaters on and stable at 40°C. Fill the hopper with the IBP:Lutrol mixture and heat the exit orifice with a heat gun until a molten material is present.

Start the extruder at 50 RPM until the product is seen exiting the exit nozzle (~1 minute). Continuously feed the mixture until all temperatures are stable then set the RPM at 250.

Continuously process the material for 5 minutes then collect the product on plastic sheet lined trays.

Additional runs were conducted using extruders with different RPM rates, L/D (25 and 15) and with and without the exit nozzle in place (lower internal forces). These runs produced products where the particles of IBP were apparently not as thoroughly coated with the eutectic, or where the eutectic was not in as intimate a contact with the crystals of IBP as the product run with the higher L/D, slower RPM or with the nozzle in place. Dissolution test result, shown in Chart 1 below also support the requirement for sufficient force and low temperatures.

Example III

Extrudate Milling

Pass the extrudant though an Apex 114 Mill with no mesh and the hammers forward. Feed the mixture very slowly at a feed rate of 4 RPM and the mill at 4590 RPM and allow the top of the feeder to clear before continuing to feed. Care should be taken to not allow the milling process to generate too much heat.

Collect the milled material and pass it through the mill again using a No. 6 screen and the same settings. Again feed the hopper very slowly to avoid excessive heat and allow the top of the feeder to clear before continuing to feed.

Example IV

Ibuprofen Dissolution Studies

Microparticles of the milled extrudate and liquiflash formed IBP:Lutrol material of Examples I - III were tested for dissolution according to the following procedure. Some results are shown in Chart 1 below.

Instrumentation:

USP 711 Apparatus 2 (paddles), operated under the following conditions:

Speed:	50 RPM
Temperature:	37.0 ± 0.5°C
Medium:	PH 5.2 Phospahate buffer, 900ml

Sampling time: 5, 10, and 20 minutes

UV Spectrophotometer:

Wavelength: 266nm

Cell Pathlength: 1.0 cm

Procedure:

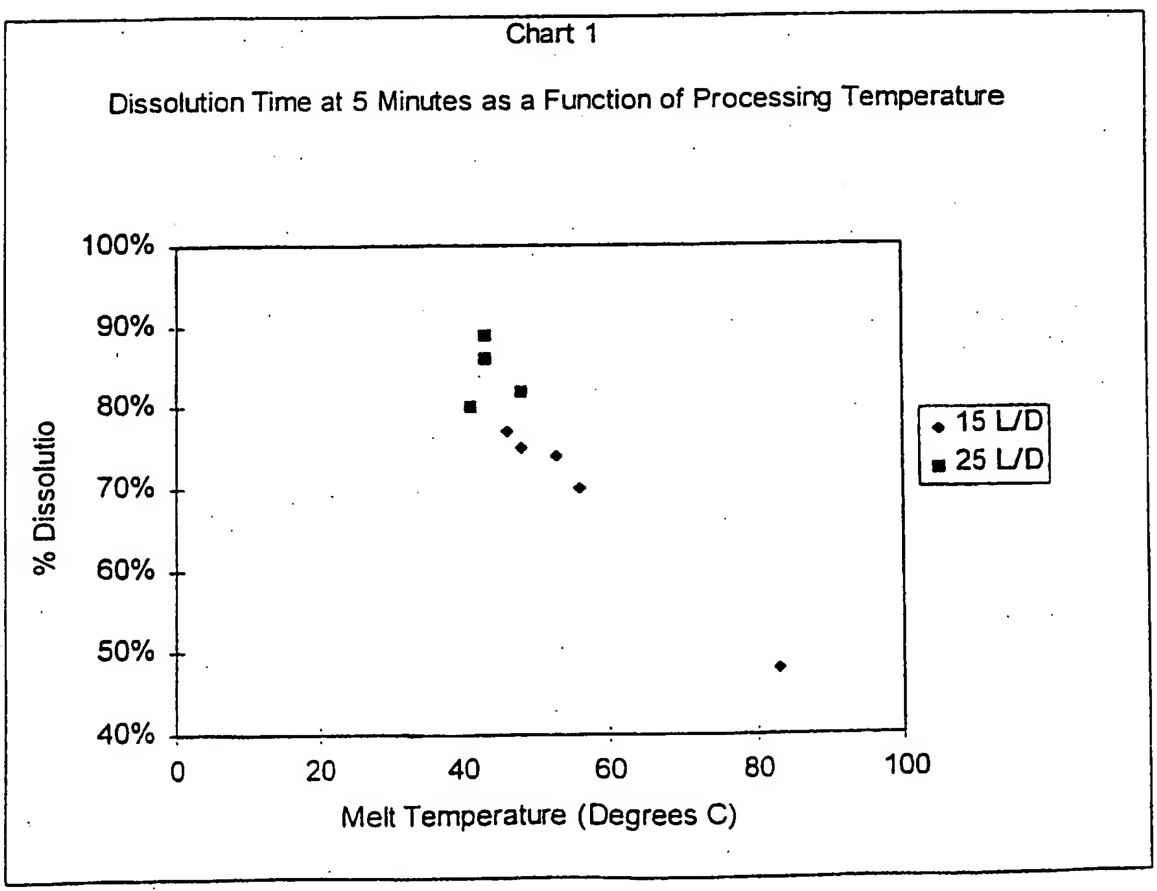
1. Dispense 900 ml of medium into each dissolution vessel.

2. Degas the medium by sparging with Nitrogen for 3 minutes.

3. Set up dissolution apparatus (Beckman/Hanson Automated Dissolution System) by verifying the height of the paddles and equipping sample probes with 10 micron pre-filters. Equilibrate the media to 37.0 ± 0.5°C.

4. Weigh out enough sample to contain 200mg of IBP. Place a sample in each vessel. Lower the apparatus to the appropriate level. Start the apparatus at the above specified parameters.

5. At the specified times point the automated instrument will draw a sample from each vessel and analyzer by the UV Spectrophotometer.



CLAIMS:

1. A method of making an active/surfactant solubilizing delivery system product the method comprising:

(a) mixing about 10 to about 95 parts of at least one particulate active agent with about 90 to about 5 parts of at least one solid solubilizing agent;

(b) processing the mixture at temperatures from below the formation temperature of a eutectic of the active agent and the solubilizing agent to below the temperature at which the active dissolves in the solubilizer and under conditions of force and residence time sufficient to produce a eutectic of the active and solubilizer and to place the eutectic in at least partial intimate contact with the particles of the active; and

(c) recovering the active/surfactant product produced.

2. The method of claim 1 which further comprises grinding or otherwise reducing the active/surfactant product into particles of a desired size.

3. The method of claim 1 wherein the particles of active and the solubilizer are mixed in a ratio of from about 30 parts to about 90 parts active and from about 70 parts to about 10 parts solubilizer.

4. The method of claim 1 wherein the particles of active and the solubilizer are mixed in a ratio of from about 40 parts to about 80 parts active and from about 60 parts to about 20 parts solubilizer.

5. The method of claim 1 wherein the active is a drug selected from the group consisting of analgesics, H2 antagonists, non-steroidal anti-inflammatory agents, anti-cholesterolemics, anti-allergy agents and anti-migraine agents.

6. The method of claim 5 wherein the drug is selected from the group consisting of analgesics.

7. The method of claim 6 wherein the analgesic is selected from the groups consisting of ibuprofen, ketoprofen and naproxen.

8. The method of claim 1 wherein the active is Ibuprofen (IBP) and the ratio of IBP to solubilizer is from about 60:40 to about 75:25

9. A solubilizing delivery system comprising particles of at least one active agent and at least one solubilizing agent in a ratio from about 10:90 to about 95:5, wherein the at least one active agent and the at least one solubilizing agent form a eutectic and the eutectic is in at least partial intimate contact with the particles of active.

10 The delivery system of claim 9 wherein the particles of active and the solubilizer are mixed in a ratio of from about 40 parts to about 80 parts active and from about 60 parts to about 20 parts solubilizer.

11. The delivery system of claim 9 wherein the active is a drug selected from the group consisting of analgesics, H2 antagonists, non-steroidal anti-inflammatory agents, anti-cholesterolemics, anti-allergy agents and anti-migraine agents.

12. The delivery system of claim 11 wherein the drug is selected from the group consisting of analgesics.

13. The delivery system of claim 12 wherein the analgesic is selected from the group consisting of ibuprofen, ketoprofen and naproxen.

14. The delivery system of claim 13 wherein the active is Ibuprofen (IBP) and the ratio of IBP to solubilizer is from about 60:40 to about 75:25.

INTERNATIONAL SEARCH REPORT

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PCT/US 98/19750

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 02017 A (ELAN CORP PLC ;CLANCY MAURICE JOSEPH ANTHONY (IE); CUMMING KENNETH) 23 January 1997 cited in the application see page 5 - page 6 ---	1-14
Y	EP 0 349 509 A (PHARLYSE SA) 3 January 1990 see page 2, line 38 - page 4, line 4 ---	1-14
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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PCT/US 98/19750

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
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